# General

## Guideline Title

Dimethyl fumarate for treating relapsing-remitting multiple sclerosis.

## Bibliographic Source(s)

National Institute for Health and Care Excellence. Dimethyl fumarate for treating relapsing-remitting multiple sclerosis. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Aug. 61 p. (Technology appraisal guidance; no. 320).

## Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

# Recommendations

## Major Recommendations

Dimethyl fumarate is recommended as an option for treating adults with active relapsing-remitting multiple sclerosis (normally defined as 2 clinically significant relapses in the previous 2 years), only if:

- They do not have highly active or rapidly evolving severe relapsing-remitting multiple sclerosis and
- The manufacturer provides dimethyl fumarate with the discount agreed in the patient access scheme.

People currently receiving treatment initiated within the National Health Service (NHS) with dimethyl fumarate that is not recommended for them by the National Institute for Health and Care Excellence (NICE) in this guidance should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

## Clinical Algorithm(s)

None provided

# Scope

## Disease/Condition(s)

Relapsing-remitting multiple sclerosis

## Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

## Clinical Specialty

Family Practice

Internal Medicine

Neurology

## Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

## Guideline Objective(s)

To assess the clinical effectiveness and cost-effectiveness of dimethyl fumarate for treating relapsing-remitting multiple sclerosis

## Target Population

Patients with relapsing-remitting multiple sclerosis

## Interventions and Practices Considered

Dimethyl fumarate

## Major Outcomes Considered

- Clinical effectiveness
  - Annualised relapse rate (ARR)
  - Symptoms of multiple sclerosis
  - Freedom from disease activity
  - Disability progression (Expanded Disability Status Scale [EDSS] score)
  - Health-related quality of life
  - Magnetic resonance imaging (MRI) outcomes
  - Adverse events of treatment
  - Mortality rate
- Cost-effectiveness

# Methodology

## Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

## Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform an assessment of the manufacturer's submission on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for this technology appraisal was prepared by Centre for Reviews and Dissemination (CRD) and Centre for Health Economics (CHE) Technology Assessment Group (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Critique of the Methods of Review(s)

*Searches*

The manufacturer's submission adequately described the search strategies used to identify relevant studies relating to the use of dimethyl fumarate for relapsing remitting multiple sclerosis (RRMS). Full details of the strategies used in each section were reported in the appendices of the submission or in the clarifications provided by the manufacturer in response to queries raised by the ERG.

Overall, the search strategies employed for each of the clinical effectiveness sections of the submission were appropriate and well documented. There were some weaknesses in the strategies, however it is unlikely that any of these would lead to relevant studies being missed by the searches. A detailed commentary on the individual searches is provided in the Appendix (sections 10.1.1 to 10.1.3) in the ERG report (see the "Availability of Companion Documents" field).

*Inclusion Criteria*

Clear inclusion criteria were stated for the systematic review of trials of dimethyl fumarate and relevant comparators. These are briefly summarised in the table below.

The study selection process was carried out in duplicate by two independent reviewers at both the initial stage of title and abstract and with full text studies; disagreements were resolved by a third reviewer. This was an appropriate method of study selection.

Table. Inclusion Criteria for Systematic Review of Trials of Dimethyl Fumarate and Specified Comparators

| | |
|---|---|
| Population | Adults aged ≥18 years with relapsing remitting multiple sclerosis (RRMS) (≥80% trial population) |
| Intervention | Licensed dose of:<br>• Interferon beta-1a<br>• Interferon beta-1b<br>• Glatiramer acetate<br>• Dimethyl fumarate*<br>• Fingolimod<br>• Natalizumab<br>• Teriflunomide |
| Comparator | Any other included intervention also at licensed dose<br>Placebo |

| | |
|---|---|
| | Best supportive care |
| Study design | Randomised controlled trials (RCTs) and non RCTs for dimethyl fumarate only |
| Other | Studies with mixed populations (disease/age) required to report subgroup data for population of interest.<br>Published before October/November 2012<br>Published in English |

*Non RCTs also eligible for dimethyl fumarate.

For population, intervention, comparator and dose, uniform inclusion criteria were used. However for study design, the inclusion criterion differed between dimethyl fumarate and the defined comparators, with non-RCTs eligible only if they assessed dimethyl fumarate.

The inclusion criteria were appropriate to the purpose of the review. The lack of requirement for blinding as a criterion was appropriate to ensuring completeness of the data set, particularly given the fact that the majority of the comparator disease modifying therapies (DMTs) are delivered by injection, and blinding is often considered inappropriate in these contexts.

The ERG asked the manufacturer to comment on the specific exclusion of alemtuzumab and laquinimod as comparators whereas the out of scope teriflunomide was included. The manufacturer's response stated that they included only licensed interventions and their approved doses for the treatment of RRMS; they stated that teriflunomide was specifically included because it received U.S. Food and Drug Administration (FDA) approval prior to the review dates. The ERG notes that the 7 mg dose of teriflunomide was included together with the FDA licensed 14 mg dose; the impact of this on results is likely to be insignificant.

The use of a language restriction, with only studies reported in English has the potential to lead to selection bias (as well as the more general omission of relevant studies) but is listed as being due to NICE preference. The ERG was unable to verify the source of this preference.

In order to verify the application of the inclusion criteria to the identified studies, the ERG requested that the manufacturer provide the list of studies excluded at full text screening, together with reasons for their exclusion. This list of studies excluded at the final stage was supplied and checked by the ERG: it did not contain any studies which should have been included. See section 4.2.5 in the ERG report for further discussion of studies excluded from the review of dimethyl fumarate and section 4.3.3 in the ERG report (see the "Availability of Companion Documents" field) for studies excluded from the mixed treatment comparison (MTC).

It was unclear from the submission whether any relevant non-RCTs of dimethyl fumarate were included (two were noted as being identified): the ERG requested clarification on either a) details of the included studies or b) justification for their exclusion. The manufacturer clarified that the two non-RCTs initially identified were subsequently assessed as not being relevant to the submission. Having assessed these studies, the ERG agreed that this decision was correct.

Cost-effectiveness

See section 10.1.4 in the ERG report (see the "Availability of Companion Documents" field) for search strategy for cost-effectiveness studies. The search strategy for cost-effectiveness studies had some minor weaknesses but overall appears to be appropriate.

## Number of Source Documents

Clinical Effectiveness

- Two phase three randomised controlled trials (RCTs) (the DEFINE and CONFIRM trials) were included in the systematic review.
- Twenty-seven additional RCTs were used for mixed treatment comparison (MTC).

Cost-Effectiveness

- No economic evaluation including dimethyl fumarate was identified in the literature.
- The manufacturer submitted an economic analysis.

## Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

## Rating Scheme for the Strength of the Evidence

Not applicable

## Methods Used to Analyze the Evidence

Meta-Analysis of Randomized Controlled Trials

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

## Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform an assessment of the manufacturer's submission on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for this technology appraisal was prepared by the Centre for Reviews and Dissemination (CRD) and Centre for Health Economics (CHE) Technology Assessment Group (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Critique of Data Extraction

The methods used for data extraction involved reasonable measures to reduce reviewer error or bias, with data entered by one reviewer, checked by a second, and disagreements resolved through discussion. The ERG checked main outcome data against published trial reports and, where appropriate, the clinical study reports supplied by the manufacturer. These were accurately reported with one exception.

Quality Assessment

The trials were assessed for quality in the manufacturer's submission using criteria which broadly reflect those of the Cochrane risk of bias tool. Items relating to blinding of patients, personnel and outcome assessors were grouped as one question although substantiation of the answers referred to all three. It was unclear whether the assessment had been conducted in duplicate. The submission assessed both the DEFINE and CONFIRM trials as meeting all these quality criteria and provided substantiation for these assessments.

The ERG replicated the quality assessments based on the totality of information available, including the published papers and protocols for the DEFINE and CONFIRM studies. The ERG's quality assessment, using the manufacturer's criteria is shown in Table 5 of the ERG report (see the "Availability of Companion Documents" field).

The ERG was in agreement with the manufacturer's overall assessment of study quality, although they did note a small difference in the completion of the checklist. The manufacturer's submission scored the blinding item with "YES", although noting that the patients enrolled in the glatiramer acetate arm were unblinded; the examining neurologist was blinded to treatment for all patients, including those receiving glatiramer acetate. In addition the ERG noted that the trial was not powered to assess the comparison between dimethyl fumarate and glatiramer acetate and that the manufacturer's assessment was accurate with respect to the placebo comparison.

Evidence Synthesis

The manufacturer also submitted a pooled analysis of DEFINE and CONFIRM dimethyl fumarate versus placebo comparisons using both fixed (Mantel-Haenszel) and random (DerSimonian and Laird) effects for the following efficacy outcomes: annualised relapse rate (ARR), ARR for steroid-treated relapses, proportion of patients with relapse at 12 months, proportion of patients with relapse at 24 months, proportion of patients remaining relapse free at 12 months, proportion of patients remaining relapse free at 24 months; change in Expanded Disability Status Scale (EDSS) score at 24 months; disability progression sustained for 3 months at 24 months, and disability progression sustained for 6 months at 24 months. Rate ratios, relative risks or weighted mean differences were presented. In the original submission the manufacturer undertook the meta-analysis for disability progression using relative risk rather than hazard ratio which was used for the individual trials and is a more appropriate analysis for confirmed disability progression. In the clarifications submitted by the manufacturer they re-ran the meta-analysis using the hazard ratio for disability progression and the ERG have used the revised analysis. The appropriateness of the pooled analysis is considered in section 4.2.3 of the ERG report (see the "Availability of Companion Documents" field).

Meta-analysis results were also presented for the safety and tolerability outcomes assessed in the two trials. These were presented in place of results for the individual RCTs: the decision to provide only pooled safety data in the submission appeared appropriate.

See section 4 of the ERG report for additional information on clinical effectiveness (see the "Availability of Companion Documents" field).

Cost-effectiveness

In the analysis presented by the manufacturer, dimethyl fumarate was compared to Rebif 22 µg, Rebif 44 µg, Avonex, Betaferon, glatiramer acetate, natalizumab and fingolimod for the general relapsing remitting multiple sclerosis (RRMS) population. The population evaluated in the model reflected the population in the dimethyl fumarate trials as discussed in section 4.2.2 of the ERG report. Although no distinction was made by the manufacturer, the comparators evaluated included both drugs recommended by NICE and licensed for first-line treatment (Rebif 22µg, Rebif 44µg, Avonex, Betaferon, glatiramer acetate) and drugs recommended and licensed for patients with rapidly evolving severe disease or patients with highly active disease (natalizumab, fingolimod). The ERG discusses this issue in sections 5.2.2 and 5.2.3 of the ERG report (see the "Availability of Companion Documents" field).

A Markov model was presented which characterised the natural history of the disease through patient progression from RRMS to secondary-progressive multiple sclerosis (SPMS). Whether a patient has RRMS or SPMS there is a possibility of disability progression, which is characterised by 10 EDSS states, 0 to 9. In addition to disability progression (i.e., get worse) RRMS patients may also regress to lower EDSS states (i.e., improve). SPMS patients cannot regress. The progression to SPMS from RRMS is independent of treatment and the likelihood of progressing varies according to the EDSS state. Patients may die at any time. The mortality rate was assumed equal for both RRMS and SPMS patients.

The drugs in the model affect the health of patients and cost to the health system through reduction in the annual relapse rate, the reduction in the annual risk of disability progression for a patient with RRMS, and through the occurrence of adverse events. Patients with SPMS do not receive treatment. Effectiveness data were obtained from a mixed treatment comparison of trials with a general RRMS population (see section 4.1.2 in the ERG report [see the "Availability of Companion Documents" field]). The time horizon of the model was 30 years. In the manufacturer's base case, the treatment effect on disability progression was assumed to wane after 2 years to 75% of the original effect for the third, fourth and fifth years of treatment, followed by 50% for every remaining year on treatment. Relapse effects and adverse events were assumed constant while on treatment.

Patients may discontinue the drug due to adverse events, by moving to an EDSS state of 7 or higher, or through progression to SPMS. Discontinuation of treatment results in the patient receiving no treatment for the remainder of the model time horizon.

See section 5 or the ERG report (see the "Availability of Companion Documents" field) for further details on cost-effectiveness analyses.

## Methods Used to Formulate the Recommendations

Expert Consensus

## Description of Methods Used to Formulate the Recommendations

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Care Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE website. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who Is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

## Rating Scheme for the Strength of the Recommendations

Not applicable

## Cost Analysis

Summary of Appraisal Committee's Key Conclusions on Cost-effectiveness

Availability and Nature of Evidence

The Committee commented that the manufacturer had submitted a model structurally similarly to models used in previous National Institute for Health and Care Excellence (NICE) technology appraisals.

Uncertainties Around and Plausibility of Assumptions and Inputs in the Economic Model

The Committee noted that the manufacturer modelled a waning of treatment effect because of the uncertain longer-term benefits of dimethyl fumarate. The Committee accepted the manufacturer's approach using the same rate of waning of effect for each treatment.

The Committee heard from the Evidence Review Group (ERG) that several publications presented the annual costs by Expanded Disability Status Scale (EDSS) state and that, although they were also based on the UK Multiple Sclerosis Survey, they varied considerably. Some of the cost items were non-medical, and so it was unclear whether these items met the NICE reference case. The Committee highlighted its disappointment that all of the sources used by the manufacturer to estimate the cost of relapse were of low methodological quality.

The Committee noted that the manufacturer and ERG were unable to explain any differences between the incremental cost-effectiveness ratios (ICERs) resulting from the manufacturer's model and from the model behind the risk-sharing scheme, and highlighted that there was still uncertainty related to the validity of the manufacturer's model.

Incorporation of Health-Related Quality-of-Life Benefits and Utility Values. Have Any Potential Significant and Substantial Health-related Benefits Been Identified That Were Not Included in the Economic Model, and How Have They Been Considered?

The Committee concluded that additional health-related quality-of-life benefits associated with oral treatment and short washout duration may not have been fully captured within the manufacturer's economic modelling.

Are There Specific Groups of People for Whom the Technology Is Particularly Cost Effective?

N/A

What Are the Key Drivers of Cost-effectiveness?

The main drivers of the ICERs were the costs of treatment, how likely a patient was to experience disease progression, the probability of stopping treatment, and the magnitude of the treatment waning effect.

Most Likely Cost-effectiveness Estimate (Given as an ICER)

The Committee stated that considerable uncertainty remained associated with identifying which of the beta interferons and glatiramer acetate are relatively more cost-effective when compared with dimethyl fumarate. The Committee also acknowledged that, when compared with dimethyl fumarate, Rebif-22 appeared to be the most cost-effective comparator in the manufacturer's analysis, and that Rebif-22 is a 'step-down' therapy for patients who cannot tolerate the higher dosage (that is, Rebif-44). Therefore, the Committee disregarded the comparison of dimethyl fumarate with Rebif-22, and considered the most plausible ICER to be based on a comparison of dimethyl fumarate with glatiramer acetate (the next most cost-effective comparator after Rebif-22) using the manufacturer's preferred scenario. The Committee concluded that, based on a comparison of dimethyl fumarate with glatiramer acetate, the most plausible ICER was likely to be below £27,700 per quality-adjusted life year (QALY) gained, taking into consideration that waning of treatment effect may have been overestimated and also the benefits not captured in the economic modelling, such as the oral administration of dimethyl fumarate and its shorter washout period.

### Method of Guideline Validation

External Peer Review

### Description of Method of Guideline Validation

Consultee organisations from the following groups were invited to comment on the draft scope, assessment report and the appraisal consultation document (ACD) and were provided with the opportunity to appeal against the final appraisal determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

## Evidence Supporting the Recommendations

### Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated for each recommendation.

The Appraisal Committee considered clinical and cost-effectiveness evidence submitted by the manufacturer of dimethyl fumarate and a review of this submission by the Evidence Review Group. For clinical effectiveness, two randomised controlled trials were the main source of evidence. For cost-effectiveness, the manufacturer's model was considered.

## Benefits/Harms of Implementing the Guideline Recommendations

### Potential Benefits

Appropriate use of dimethyl fumarate for treating relapsing-remitting multiple sclerosis

### Potential Harms

The summary of product characteristics lists the following adverse reactions for dimethyl fumarate: 'gastroenteritis, lymphopenia, leukopenia, hypersensitivity, burning sensation, flushing, hot flush, diarrhoea, nausea, abdominal pain, vomiting, dyspepsia, gastritis, gastrointestinal disorder, pruritus, rash, erythema, proteinuria, feeling hot, ketones measured in urine, albumin urine present, aspartate aminotransferase increased, alanine aminotransferase increased and white blood cell count decreased'.

For full details of adverse reactions and contraindications, see the summary of product characteristics.

# Contraindications

## Contraindications

For full details of adverse reactions and contraindications, see the summary of product characteristics.

# Qualifying Statements

## Qualifying Statements

- This guidance represents the views of the National Institute for Health and Care Excellence (NICE) and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

# Implementation of the Guideline

## Description of Implementation Strategy

- Section 7(6) of the National Institute for Health and Care Excellence (NICE) (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, National Health Service (NHS) England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has relapsing-remitting multiple sclerosis and the doctor responsible for their care thinks that dimethyl fumarate is the right treatment, it should be available for use, in line with NICE's recommendations.
- The Department of Health and the manufacturer have agreed that dimethyl fumarate will be available to the NHS with a patient access scheme which makes dimethyl fumarate available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the manufacturer to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to the Biogen Idec medical information team on 0800 008 7401 or by email at biogenidec@professionalinformation.co.uk.
- NICE has developed tools to help organisations put this guidance into practice. These are available on the NICE Web site .
    - Costing template and report to estimate the national and local savings and costs associated with implementation.

## Implementation Tools

Mobile Device Resources

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

# Institute of Medicine (IOM) National Healthcare Quality Report Categories

## IOM Care Need

Living with Illness

## IOM Domain

Effectiveness

Patient-centeredness

# Identifying Information and Availability

## Bibliographic Source(s)

National Institute for Health and Care Excellence. Dimethyl fumarate for treating relapsing-remitting multiple sclerosis. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Aug. 61 p. (Technology appraisal guidance; no. 320).

## Adaptation

Not applicable: The guideline was not adapted from another source.

## Date Released

2014 Aug

## Guideline Developer(s)

National Institute for Health and Care Excellence (NICE) - National Government Agency [Non-U.S.]

## Source(s) of Funding

National Institute for Health and Care Excellence (NICE)

## Guideline Committee

Appraisal Committee

## Composition of Group That Authored the Guideline

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## Financial Disclosures/Conflicts of Interest

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

## Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

## Guideline Availability

Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site .

## Availability of Companion Documents

The following are available:

- Dimethyl fumarate for treating relapsing–remitting multiple sclerosis. Costing report. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Aug. 11 p. (Technology appraisal guidance; no. 320). Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site .
- Dimethyl fumarate for treating relapsing–remitting multiple sclerosis. Costing template. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Aug. (Technology appraisal guidance; no. 320). Electronic copies: Available from the NICE Web site .
- Norman G, Rice S, O'Connor J, Lewis-Light K, Craig D, McDaid C. Dimethyl fumarate for treating relapsing-remitting multiple sclerosis: a single technology appraisal. York (UK): CRD and CHE Technology Assessment Group; 2013. 151 p. Electronic copies: Available from the NICE Web site .

## Patient Resources

The following is available:

- Dimethyl fumarate for treating relapsing-remitting multiple sclerosis. Information for the public. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Aug. (Technology appraisal guidance; no. 320). Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site . Also available for download as an eBook or ePub from the

NICE Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

## NGC Status

This NGC summary was completed by ECRI Institute on October 22, 2014.

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